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(21) International Application Number: PCT/US99/01776 (22) International Filing Date: 28 January 1999 (28.01.99) (30) Priority Data: 09/016,252 30 January 1998 (30.01.98) US (71) Applicant: PENTECH PHARMACEUTICALS, INC. [US/US]; Suite 257, 1110 Lake Cook Road, Buffalo Grove, IL 60089 (US). (72) Inventors: EL-RASHIDY, Ragab; 130 Exmoor Court, Deer- field, IL 60015 (US). RONSEN, Bruce; 1414 Keystone Avenue, River Forest, IL 60305 (US). (74) Agents: CEPURITIS, Talivaldis et al.; Olson & Hiertl, Ltd., 36th floor, 20 North Wacker Drive, Chicago, IL 60606 (US).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: TREATMENT OF FEMALE SEXUAL DYSFUNCTION (57) Abstract <p>Sexual dysfunction in human females can be ameliorated, without substantial undesirable side effects, by sublingual administration of apomorphine dosage forms. Administration of apomorphine increases nerve stimulated clitoral intracavernosal blood flow and vaginal wall blood flow for enhanced clitoral erection and vaginal engorgement in a female. A plasma concentration of apomorphine of no more than about 5.5 nanograms per milliliter is preferably maintained.</p>		

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TREATMENT OF FEMALE SEXUAL DYSFUNCTION

Field of the Invention

This invention relates to dosage forms and methods for ameliorating female sexual dysfunction. More particularly, this invention relates to the use of
5 apomorphine-containing compositions for amelioration of female sexual dysfunction.

Background of the Invention

Apomorphine is a selective dopamine receptor agonist that has been widely utilized as an emetic agent, sedative, antiparkinsonian agent and a behavior altering agent. Recent research and clinical studies have demonstrated that in males
10 apomorphine has an erectogenic effect manifested by penile erection. The effect of apomorphine on female sexual functionality has not been previously investigated.

Females also can have sexual dysfunction that increases with age and is associated with the presence of vascular risk factors and onset of menopause. Some of the vascular and muscular mechanisms that contribute to penile erection in the
15 male are believed to be similar vasculogenic factors in female genital response. It is known that in women, sexual arousal is accompanied by arterial inflow which engorges the vagina and increases vaginal lubrication and that the muscles in the perineum assist in achieving clitoral erection.

In the female, sexual dysfunction can arise from organic and psychogenic
20 causes or from a combination of the foregoing. Female sexual dysfunction includes a failure to attain or maintain vaginal lubrication-swelling responses of sexual excitement until completion of the sexual activity. Organic female sexual dysfunction is known to be related in part to vasculogenic impairment resulting in inadequate blood flow, vaginal engorgement insufficiency and clitoral erection insufficiency.

25 Female sexual dysfunction has not been studied as extensively as male sexual dysfunction. This has partly been due to the difficulty of obtaining volunteer female subjects and to the historical belief that female sexual dysfunction was orgasmic-related (delayed or non-orgasmic) or libido and hence lacked an appropriate animal model.

30 The use of New Zealand White male rabbits as animal models for impotence has been well established. More recently, studies have reported that New Zealand White female rabbits are also suitable, relatively inexpensive animal models for studying the vascular pathology in female sexual dysfunction and have shown that

vaginal engorgement and clitoral erection depend on blood inflow. See, for example, Park et al, "Vasculogenic female sexual dysfunction: the hemodynamic basis for vaginal engorgement insufficiency and clitoral erectile insufficiency," International Journal of Impotence Research, 9, (1), 27-37 (Mar. 1997).

5 In medically managing vasculogenic sexual dysfunction, a female patient needs to have her discomfort or dysfunction reduced for sexual functioning. For psychogenic sexual dysfunction management, psychological sex therapy can also be employed to help the patient.

Apomorphine previously was shown to have very poor oral bioavailability.
10 See, for example, Baldessarini et al., in Gessa et al., (eds.), Apomorphine and Other Dopaminomimetics, Basic Pharmacology, 1, 219-228, Raven Press, N.Y. (1981).

More recently, studies with males show that oral administration of apomorphine can be used to induce an erection in a psychogenic male patient, as long as the apomorphine dose required to achieve a significant erectile response is not
15 accompanied by nausea and vomiting or other serious undesirable side effects such as arterial hypotension, flushing and diaphoresis. See U.S. Patent No. 5,624,677 to El-Rashidy et al. and Heaton et al., Urology, 45, 200-206 (1995). The specific mechanisms by which apomorphine acts to produce an erectile response in a human patient are not yet completely understood but are believed to be centrally acting
20 through dopamine receptor stimulation in the medial preoptic area of the brain.

It has now been found that certain controlled delivery systems for apomorphine can provide a practical therapeutic use in ameliorating sexual dysfunction in human females while reducing the likelihood of undesirable side effects.

Summary of the Invention

25 Administration of apomorphine increases nerve stimulated clitoral intracavernosal blood flow and vaginal wall blood flow, each of which is associated respectively with enhanced clitoral erection and vaginal engorgement in a female.

A sublingual apomorphine dosage form, usually containing about 2 to about 12 milligrams, preferably about 2 to about 8 milligrams, of apomorphine, is effective for
30 producing sexual readiness in human females without inducing substantial nausea or other undesirable side effects. Sublingually, administration is effected preferably about 15 to about 20 minutes prior to sexual activity. The plasma concentration of apomorphine is maintained at no more than about 5.5 nanograms per milliliter,

preferably about 0.3 to about 4 nanograms per milliliter, and more preferably about 1 to about 2 nanograms per milliliter, to maintain a circulating serum level and mid-brain tissue level of apomorphine during the period of sexual activity sufficient to maintain vaginal engorgement, its associated lubrication and clitoral erection during coitus, but less than the amount that induces substantial nausea.

Brief Description of the Drawings

In the drawings,

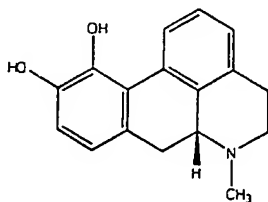
FIGURE 1 is a bar graph depicting the effect of apomorphine on female rabbit clitoral blood flow in milliliters per minute per 100 grams tissue before and after nerve stimulation for placebo and intravenous apomorphine amounts of 0.05, 0.1, 0.2, 0.3 and 0.4 milligrams per kilogram body weight;

FIGURE 2 is a bar graph depicting the effect of apomorphine on female rabbit vaginal wall blood flow in milliliters per minute per 100 grams tissue before and after nerve stimulation for placebo and intravenous apomorphine amounts of 0.05, 0.1, 0.2, 0.3 and 0.4 milligrams per kilogram body weight; and

FIGURE 3 is a graph depicting the effect of intravenous apomorphine on female rabbit systemic (diastolic and systolic) arterial pressure.

Detailed Description of Preferred Embodiments

Apomorphine can be represented by the following formula



and exists in a free base form or as an acid addition salt. For the purposes of the present invention apomorphine hydrochloride is preferred; however, other pharmacologically acceptable moieties thereof can be utilized as well. The term "apomorphine" as used herein includes the free base form of this compound as well as the pharmacologically acceptable acid addition salts thereof. In addition to the hydrochloride salt, other acceptable acid addition salts are the hydrobromide, the hydroiodide, the bisulfate, the phosphate, the acid phosphate, the lactate, the citrate, the tartrate, the salicylate, the succinate, the maleate, the gluconate, and the like.

Apomorphine is a dopamine receptor agonist that has a recognized use as an emetic when administered subcutaneously in about a 5-milligram dose. For the purposes of the present invention, apomorphine or a similarly acting dopamine receptor agonist is administered in an amount sufficient to excite cells in the mid-
5 brain region of the patient but with minimal side effects. This cell excitation is believed to be part of a cascade of stimulation that is likely to include neurotransmission with serotonin and oxytocin.

It is known from studies with males that the dopamine receptors in the mid-brain region of a male patient can be stimulated to a degree sufficient to cause an
10 erection by the sublingual administration of apomorphine so as to maintain a plasma concentration of apomorphine of no more than about 5.5 nanograms per milliliter (5.5 ng/ml).

The pharmacokinetics of apomorphine are the same for both female and males, based on apomorphine hydrochloride studies with humans (Parkinson's disease) and
15 animals reported in the literature. Thus, the onset and duration of effect from a given dose of apomorphine in men compared to animals applies to females as well.

It was found that an intravenous dosage of apomorphine of about 100 micrograms per kilogram ($\mu\text{g/kg}$) of body weight was optimum for producing a vasculogenic effect on nerve stimulated vaginal and clitoral blood flow in female
20 rabbit studies. For human females, this dosage correlates to an optimum dosage of about 1/10 or 10 $\mu\text{g/kg}$ of body weight. In sublingual tablet forms, the bioavailability of apomorphine is about 13% compared to subcutaneously administered apomorphine hydrochloride. Assuming an average female body weight
25 of about 70 kilograms, a significant sexual readiness dose of apomorphine would be about 76 $\mu\text{g/kg}$ or about a 5.3 milligram (mg) tablet. A dosage range of about 2 mg to about 12 mg, therefore, would produce sexual readiness (i.e., clitoral erectogenesis and vaginal engorgement on sexual stimulation) in women.

Sublingual administration preferably takes place over a time period in the range of about 2 to about 10 minutes, or longer, more preferably about 15 to about
30 20 minutes prior to sexual activity. The amount of apomorphine administered sublingually over this time period preferably is in the range of about 25 $\mu\text{g/kg}$ of body weight to about 80 $\mu\text{g/kg}$ of body weight.

Illustrative preferred sublingual dosage forms are set forth in Table I, below.

TABLE I

150 Milligram Apomorphine Hydrochloride Sublingual Tablets

	<u>3-mg Tablet</u>	
	Apomorphine Hydrochloride	2.00 wt-%
5	Mannitol	66.67 wt-%
	Ascorbic Acid	3.33 wt-%
	Citric Acid	2.00 wt-%
	Avicel PH102	15.00 wt-%
	Methocel E4M	10.00 wt-%
10	Aspartame	0.67 wt-%
	Magnesium Stearate	0.33 wt-%
	<u>4-mg Tablet</u>	
	Apomorphine Hydrochloride	2.66 wt-%
	Mannitol	66.00 wt-%
15	Ascorbic Acid	3.33 wt-%
	Citric Acid	2.00 wt-%
	Avicel PH102	15.00 wt-%
	Methocel E4M	10.00 wt-%
	Aspartame	0.67 wt-%
20	Magnesium Stearate	0.33 wt-%
	<u>5-mg Tablet</u>	
	Apomorphine Hydrochloride	3.33 wt-%
	Mannitol	65.34 wt-%
	Ascorbic Acid	3.33 wt-%
25	Citric Acid	2.00 wt-%
	Avicel PH102	15.00 wt-%
	Methocel E4M	10.00 wt-%
	Aspartame	0.67 wt-%
30	Magnesium Stearate	0.33 wt-%

If desired, and in order to facilitate absorption and thus bioavailability, the presently contemplated dosage forms can also contain, in addition to tableting excipients, β -cyclodextrin or a β -cyclodextrin derivative such as hydroxypropyl- β -cyclodextrin (HPBCD). Illustrative dosage forms containing HPBCD are shown in Tables II and III, below.

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TABLE II
Apomorphine Hydrochloride Sublingual Tablets
With Hydroxypropyl- β -Cyclodextrin

		<u>mg/Tab</u>
5	Apomorphine Hydrochloride	4.0
	HPBCD	5.0
	Ascorbic Acid	10.0
	PEG8000	39.5
10	Mannitol	39.5
	Aspartame	<u>2.0</u>
	TOTAL	100.0

TABLE III
Apomorphine Hydrochloride Sublingual
Tablets With β -Cyclodextrin

		<u>mg/Tab</u>
15	Apomorphine Hydrochloride	5.0
	β -Cyclodextrin	20.0
20	Ascorbic Acid	5.0
	Mannitol	68.9
	Magnesium Stearate	1.0
	D&C Yellow 10 Aluminum Lake	<u>0.1</u>
25	TOTAL	100.0

The onset of nausea can be obviated or delayed by delivering apomorphine at a controlled dissolution rate so as to provide circulating serum levels and mid-brain tissue levels of apomorphine sufficient for vaginal and clitoral engorgement without inducing nausea. When apomorphine is administered at or near the relatively higher amounts of the aforementioned dosage range, the likelihood of nausea onset can be reduced by concurrent administration of a ganglionic agent (inhibitor of ganglionic response) such as nicotine or lobeline sulfate. For this purpose, the weight ratio of apomorphine to ganglionic agent is in the range of about 10 to about 1.

Other antiemetic agents that can be used in conjunction with apomorphine are antidopaminergic agents such as metoclopramide, and the phenothiazines, e.g., chlorpromazine, prochlorperazine, pipamazine, thiethylperazine, oxypendyl hydrochloride, and the like. Also suitable are the serotonin (5-hydroxytryptamine or 5-HT) antagonists such as domperidone, ondansetron (commercially available as the

hydrochloride salt under the designation Zofran®), and the like, the histamine antagonists such as buclizine hydrochloride, cyclizine hydrochloride, dimenhydrinate (Dramamine), and the like, the parasympathetic depressants such as scopolamine, and the like, as well as other anti-emetics such as metopimazine, trimethobenzamide, benzquinamine hydrochloride, diphenidol hydrochloride, and the like.

Nicotine-containing dosage forms and domperidone-containing dosage forms are illustrated in Table IV, below.

TABLE IV
Apomorphine Hydrochloride Sublingual Tablets
Containing an Anti-Emetic Agent

	<u>mg/Tab</u>
Apomorphine Hydrochloride	5.0
Ascorbic Acid	5.0
Mannitol	67.9
Magnesium Stearate	1.0
Nicotine	1.0
β -Cyclodextrin	20.0
D&C Yellow 10 Aluminum Lake	<u>0.1</u>
TOTAL	100.0

	<u>mg/Tab</u>
Apomorphine Hydrochloride	5.0
Ascorbic Acid	5.0
Mannitol	58.9
Magnesium Stearate	1.0
Domperidone	10.0
β -Cyclodextrin	20.0
D&C Yellow 10 Aluminum Lake	<u>0.1</u>
TOTAL	100.0

The preferred sublingual dosage forms dissolve within a time period of at least about 2 minutes but preferably less than about 10 minutes. The dissolution time can be longer, however, if desired as long as the necessary plasma concentration of apomorphine can be maintained. More preferably, the dissolution time in water for the presently contemplated dosage forms is about 3 minutes to about 5 minutes.

The following examples further illustrate the vasculogenic effect of apomorphine on vaginal and clitoral blood flow in females, employing an appropriate female animal model.

Methods

5 New Zealand White female rabbits (n=6, about 3.5-4 kg) were anesthetized with intravenous administration of pentobarbital. A 20 gauge angiocatheter was placed into the right carotid artery for measurement of systemic arterial pressure. A midline abdominal incision was made and the pelvic nerve branch to the vagina and clitoris was dissected. Nerve stimulation was performed with a Harvard subminiature
10 electrode placed around the pelvic nerve branch to the vagina and clitoris and connected to a Grass SD-9 stimulator. Clitoral intracavernosal and vaginal wall blood flow were measured with a laser Doppler flow probe placed directly into the clitoral cavernosal tissue or into the vaginal wall and connected to a laser Doppler flowmeter.

15 Basal arterial blood pressure and clitoral and vaginal blood flow were each recorded before and then after stimulation of the pelvic nerve branch to the clitoris and vagina. After this, apomorphine was administered through the ear vein in a dose response manner (0.05 mg/kg, 0.1 mg/kg, 0.2 mg/kg, 0.3 mg/kg and 0.4 mg/kg). The effect of apomorphine administration on arterial blood pressure and clitoral and
20 vaginal blood flow were each recorded before and then after nerve stimulation.

Results

1. Effect of apomorphine on clitoral intracavernosal blood flow.

Stimulation of the pelvic nerve branch to the vagina and clitoris caused a significant increase in clitoral intracavernosal blood flow. Intravenous administration
25 of apomorphine did not affect baseline clitoral intracavernosal blood flow. Intravenous administration of apomorphine at concentrations of 0.05 mg/kg to 0.2 mg/kg caused a concentration dependent increase in nerve stimulation-induced peak clitoral intracavernosal blood flow, as depicted graphically in Figure 1. In particular, apomorphine at 0.1 mg/kg, 0.2 mg/kg and 0.3 mg/kg caused a statistically significant
30 increase in nerve stimulation-induced peak clitoral intracavernosal blood flow compared to that observed before apomorphine administration (Figure 1).

2. Effect of apomorphine on vaginal wall blood flow.

Intravenous administration of apomorphine did not affect basal vaginal wall blood flow. Apomorphine at concentrations of 0.05 and 0.2 mg/kg caused a concentration dependent increase in nerve stimulation-induced peak vaginal wall blood flow, as graphically depicted in Figure 2. Intravenous administration of 0.1 and 0.2 mg/kg apomorphine caused a statistically significant increase in nerve stimulation-induced peak vaginal wall blood flow compared to that observed before apomorphine administration (Figure 2).

Apomorphine at concentration of 0.4 mg/kg produced an adverse effect on nerve stimulation-induced increase in vaginal wall blood flow.

3. Effect of apomorphine on systemic arterial pressure.

The effect of increasing doses of apomorphine on diastolic arterial pressure is shown in Figure 3. Intravenous administration of apomorphine caused a concentration dependent moderate decrease in diastolic arterial pressure while having minimal effect on systolic arterial pressure.

Conclusion

Intravenous administration of apomorphine at a concentration of 0.1 mg/kg, 0.2 mg/kg and 0.3 mg/kg caused a significant increase in nerve stimulation-induced peak clitoral intracavernosal blood flow. Intravenous administration of apomorphine at a concentration of 0.1 mg/kg and 0.2 mg/kg caused a significant increase in vaginal wall blood flow. The main side effect of intravenous administration of apomorphine noted was a moderate decrease in diastolic blood pressure. A dose of about 0.1 mg/kg was judged optimal.

Studies with this female rabbit model showed that the hemodynamic mechanisms of clitoral erection and vaginal engorgement depend on the relaxation of clitoral cavernosal and vaginal wall smooth muscle. It is also known that in the female human, vasocongestion of the vagina entails lubrication of the vagina and swelling of the external genitalia during sexual excitation. Thus, the enhancement of clitoral blood flow by apomorphine in the female rabbit was judged indicative of improving clitoral erection and the enhancement of vaginal blood flow by apomorphine was judged indicative of increasing vaginal lubrication and augmenting vaginal engorgement in human females.

It is known that dosage ranges with apomorphine hydrochloride are species dependent. In humans, the effective dosage compared to animals is about 1/10. Thus, an optimum dose of about 0.1 mg/kg given intravenously, based on the female rabbit study would correlate to an effective dose of about 0.01 mg/kg in a human female. Since sublingual administration of apomorphine is known to provide about 13% bioavailability compared to subcutaneous administered apomorphine, a dosage of about 76 micrograms/kg or about 5.3 mg tablet for a 70 kg weight woman would produce a significant sexual readiness (clitoral erectogenesis and vaginal engorgement on sexual stimulation). Thus, a dosage range of about 2 to about 12 mg, preferably about 2 to about 8 mg., more preferably about 4 to about 6 mg. is sufficient for producing sexual readiness in women without inducing substantial nausea.

The foregoing discussion and the reported studies are intended as illustrative of the present invention and are not to be taken as limiting. Still other variants within the spirit and scope of this invention are possible and will readily present themselves to those skilled in the art.

WE CLAIM:

1. A method of ameliorating sexual dysfunction in a human female which comprises administering to said female apomorphine or a pharmaceutically acceptable acid addition salt thereof as a sublingual dosage form and in an amount sufficient to
5 increase intracitoral blood flow and vaginal wall blood flow on stimulation of said female but less than the amount that induces substantial nausea.
2. The method in accordance with claim 1 wherein the sublingual dosage form contains about 2 milligrams to about 12 milligrams of apomorphine.
3. The method in accordance with claim 1 wherein the amount of
10 apomorphine administered is in the range of about 25 to about 80 micrograms per kilogram of body weight.
4. The method in accordance with claim 1 wherein the apomorphine is administered as the hydrochloride salt.
5. The method in accordance with claim 1 wherein the apomorphine is
15 administered together with a β -cyclodextrin.
6. The method in accordance with claim 1 wherein the β -cyclodextrin is hydroxypropyl- β -cyclodextrin.
7. A method of stimulating dopamine receptors in the mid-brain region of a human female to cause clitoral erectogenesis and vaginal engorgement which
20 comprises administering to the female apomorphine in a sublingual dose containing about 25 to about 80 micrograms of apomorphine per kilogram of body weight and at a rate so as to maintain a plasma concentration of apomorphine of no more than about 5.5 nanograms per milliliter during sexual activity.
8. The method in accordance with claim 7 wherein the plasma
25 concentration of apomorphine is maintained in the range of about 0.3 to about 4 nanograms per milliliter during sexual activity.
9. The method in accordance with claim 7 wherein the plasma concentration of apomorphine is maintained in the range of about 1 to about 2 nanograms per milliliter during sexual activity.
- 30 10. A method of ameliorating sexual dysfunction in a human female which comprises administering to said female apomorphine or a pharmaceutically acceptable acid addition salt thereof sublingually prior to sexual activity, and in an amount sufficient to stimulation induce clitoral erectogenesis and vaginal engorgement and to

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maintain a plasma concentration of apomorphine at a level of no more than about 5.5 nanograms per milliliter

11. The method in accordance with claim 10 wherein the plasma concentration of apomorphine is maintained at a level of about 0.3 to about 4
5 nanograms per milliliter,

12. The method in accordance with claim 10 wherein the plasma concentration of apomorphine is maintained at a level of about 1 to about 2 nanograms per milliliter.

13. The method in accordance with claim 10 wherein the amount of
10 apomorphine administered is in the range of about 2 milligrams to about 12 milligrams.

14. The method in accordance with claim 10 wherein the amount of apomorphine administered is in the range of about 25 to about 80 micrograms per kilogram of body weight.

15 15. The method in accordance with claim 10 wherein apomorphine is administered as the hydrochloride salt.

16. The dosage form in accordance with claim 10 additionally containing a β -cyclodextrin.

17. The dosage form in accordance with claim 16 wherein the β -
20 cyclodextrin is hydroxypropyl- β -cyclodextrin.

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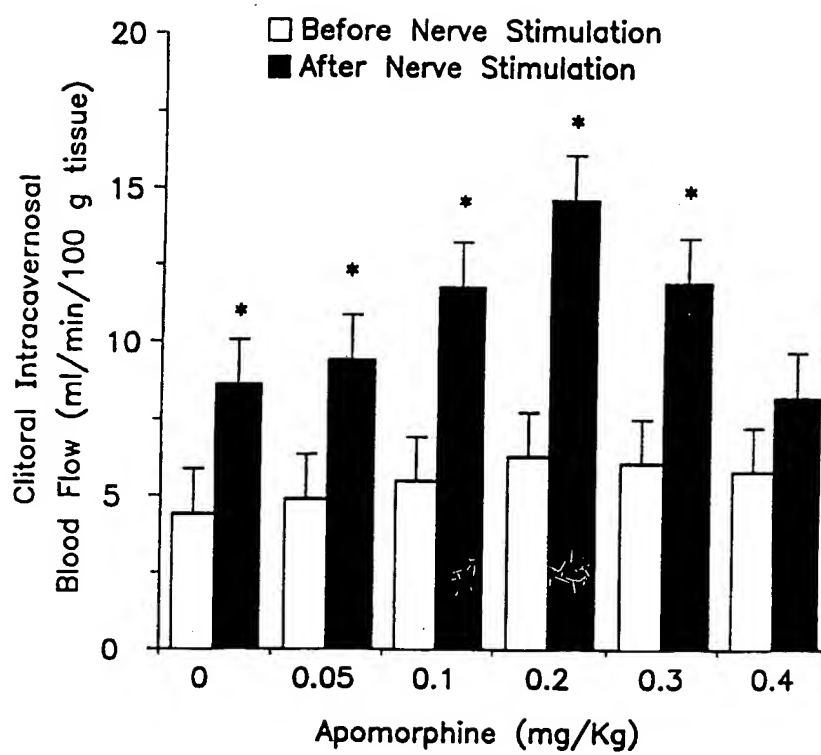


FIG. 1

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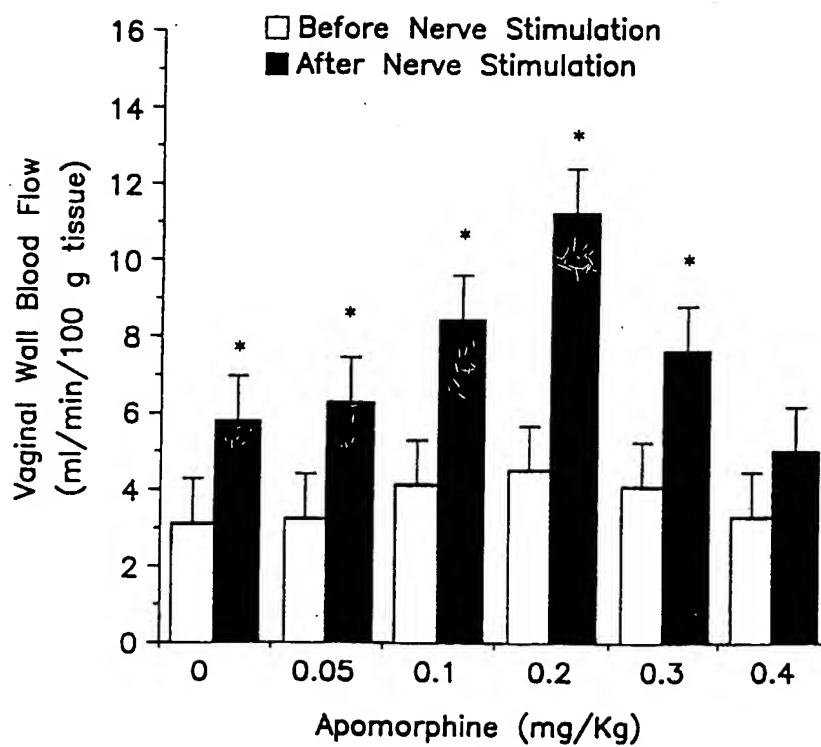


FIG. 2

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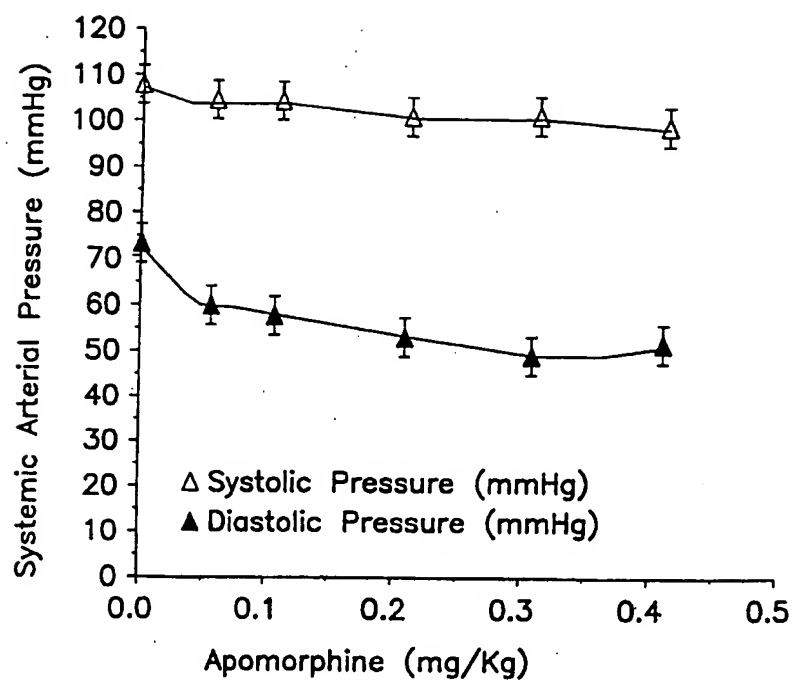


FIG. 3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/01776

A. CLASSIFICATION OF SUBJECT MATTER IPC(6) : A61F 6/06 US CL : 424/430 According to International Patent Classification (IPC) or to both national classification and IPC														
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